Guidance for Industry and FDA Staff

Clinical Trial Considerations: Vertebral Augmentation Devices to Treat Spinal Insufficiency Fractures

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Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Contains Nonbinding Recommendations

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This guidance document represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance document. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance document.

1. Introduction

This guidance document provides you with information regarding clinical studies for devices used in spinal vertebral body augmentation for the purpose of treating insufficiency fractures of the spinal vertebral body due to minor trauma, osteoporosis, or other lytic conditions. Devices used in spinal vertebral body augmentation include polymethylmethacrylate (PMMA) based bone cements, classified under 21 CFR 888.3027, class II (special controls). FDA has designated the guidance document entitled **Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement**[1] as the special control for this device. As described in that guidance, in some instances FDA recommends clinical studies to support a new material or change to an existing formulation. Whether FDA recommends that you conduct a clinical study depends on how significantly different your material or formulation is from those of devices we have cleared for the same intended use.

It is likely in the future that different materials such as resorbable and permanent polymers, and other types of materials may be injected into the vertebral body for the purpose of stabilizing the fractured spinal vertebral body in spinal augmentation procedures. The purpose of this guidance is to provide information related to clinical studies FDA may recommend in the support of premarket notification submissions (510(k)s) for these devices.

This guidance document augments the **Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement**[1] and to the discussion of clinical investigational plans in the guidance entitled **Guidance Document for the Preparation of IDEs**

[1] http://www.fda.gov/cdrh/ode/guidance/668.html

for Spinal Systems.[2] Please refer to it for FDA's recommendations about the statistical analysis of studies of these devices.

This guidance document does not include fusion or non-fusion devices (e.g., vertebral body replacement devices, spacers, internal or external fixation devices, or cages). See also **Guidance for Spinal System 510(k)s**[3] and 21 CFR §§ 888.3050, 888.3060, 888.3070.

FDA's guidance documents, including this guidance document, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe should be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the document, **A Suggested Approach to Resolving Least Burdensome Issues**. It is available on our Center web page at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM588914.pdf

2. Clinical Indications

There are two common types of compression fractures where vertebral augmentation devices may be indicated for use:

Compression fractures secondary to trauma due to osteoporosis of the spine

Stable fractures due to minor trauma in patients with osteoporotic bone may be treated with conservative care. Those that are recalcitrant to medical therapy may require surgical intervention. In designing a study for this indication, we recommend that you give special attention to the type of fracture/degree of instability, level of fracture, percent retropulsion into the spinal canal, and the number of levels involved. For the majority of these fractures, the conditions listed in the definition below apply. If neurological or spinal canal compromise is evident, percutaneous treatment may not be appropriate.

Insufficiency (compression) fractures secondary to osteoporosis or other lytic etiology

These fractures occur due to normal forces incurred by the spine during a person's activities of daily living in bone that is insufficient as a result of osteoporosis or other lytic bone conditions. There is a growing body of literature describing devices that are used for the treatment of insufficiency fractures due to neoplasm or osteoporosis, either for stabilization or reduction of the fracture. These devices include high and low modulus bone cements,

[2] http://www.fda.gov/cdrh/ode/87.pdf
[3] http://www.fda.gov/cdrh/ode/guidance/636.html

some resorbable and permanent polymers, and other types of materials injected into the vertebral body for the purpose of stabilizing the fractured spinal vertebral body bone in spinal augmentation procedures.

3. Surgical Procedures

Vertebral augmentation procedures attempt to stabilize the spine or reduce vertical compression by adding material to the spine. Two vertebral augmentation procedures that involve devices[4] are vertebroplasty and kyphoplasty.

Vertebroplasty

In vertebroplasty, the material is placed directly into the fracture site to attempt to stabilize the site. This procedure may involve no manipulation or only external reduction by extension, i.e., physical manipulation of the patient when placing the patient on the operating table before the material is injected into the fracture site.

Kyphoplasty

Kyphoplasty is so named because it involves the attempt to reduce the kyphosis that results from vertebral body collapse. In kyphoplasty, a surgical instrument is used to reduce the collapsed vertebral body towards its original shape. The material is then placed in the vertebral body and the instrument removed, leaving the material in place to stabilize the reduction.

4. Clinical Investigational Plan

In addition to the recommendations described in **Guidance Document for the Preparation of IDEs for Spinal Systems**,[5] we recommend that you include the following when designing your investigational plan for these types of devices.

A. Choice of Control

We recommend that you incorporate a concurrent, randomized control to minimize the potential for bias and confounding factors which may affect the study outcomes. This may include the use of accepted alternative treatments, for example, legally marketed devices, specialized physical therapy, medication and bracing, a sham procedure using an analgesic, or other control methods. If you conduct a sham procedure, we recommend that you include a sufficient number of patients in your sample size to adjust for the number of patients generally expected to experience a placebo effect. FDA recognizes that it may be difficult for sponsors to develop a clinical study design with a sham control arm that both investigators and patients believe is ethical; for this reason, studies involving a sham control arm should be carefully designed with due consideration to risks versus benefits. Although crossover studies are possible (e.g., at 6 weeks), we recommend that you demonstrate that the analysis at the time of crossover is valid to determine the safety and effectiveness of the product. In most instances, FDA will request safety and effectiveness

[4] Materials used for these purposes are devices.
[5] http://www.fda.gov/cdrh/ode/87.pdf

data for an adequate number of patients at the study completion for both the investigational and control groups.

We also recommend that you define specific pain, function, and/or radiographic criteria that identify control patients who would qualify for crossover to the treatment group.

B. Inclusion and Exclusion Criteria

When establishing inclusion and exclusion criteria, we recommend that you include the following:

- location of fractures
- age and medical status (co-morbidities) of patients
- the percentage of compression
- number of involved levels
- baseline pain and function levels for inclusion
- radiographic evaluation
- neurologic status
- preoperative venograms
- instability and other excluded conditions.

You should also identify any other criteria you intend to use for entry into the study. For example, we recommend that your inclusion and exclusion criteria reflect the following:

Percent Compression

We recommend that you base the percent compression on the adjacent normal vertebral body and exclude the *vertebra plana*.

Involved Levels

We recommend that you state the number of involved levels to be treated. Because the treatment of several levels at one time has been associated with greater morbidity, we recommend excluding subjects with more than 3 levels needing treatment at one time.

Pain and Function Levels

We recommend that you state the minimum pain and function scores that will characterize a patient for inclusion in the study. You should assess pain and function by numerical scoring on validated scales.

Radiographic and Other Imaging Evaluations

We recommend that you assess patients by radiographic or other imaging methods, e.g., computed tomography (CT) scan, magnetic resonance imaging (MRI). We also recommend that you use bone scans or other appropriate imaging methods to define the levels of acute fracture.

Preoperative Venograms

We recommend that you use preoperative venograms to assess the surrounding vascular structures for devices with material properties different than currently cleared devices.

Instability and Other Excluded Conditions

We recommend that you exclude subjects with instability indicated by any one of the following:

- neurologic deficit
- kyphosis >30°
- compression >50%
- translation >4 mm
- interspinous-process widening.

We recommend that you exclude subjects with conditions that warrant open decompression and therefore are not appropriate for (percutaneous) vertebroplasty or reduction osteoplasty. For example:

- spinal canal or neural foramen compromise
- cortical disruption
- burst fractures
- pedicle fractures.

We also recommend that you exclude subjects with confounding factors or conditions. For example:

- asymptomatic, stable or improving levels (e.g., prophylactic treatment)
- infection
- myelopathy
- coagulopathy
- allergy to device materials
- radiculopathy symptoms
- pregnancy
- high energy trauma
- severe cardiopulmonary deficiencies.

Because osteoporotic compression fractures have historically been successfully treated with conservative care, we recommend you consider an appropriate inclusion criterion so as to select patients that have failed various, currently available conservative treatments, after a sufficient time period when fractures would be expected to heal, generally 8 weeks or more. Conservative treatment may include analgesia, bed rest, and bracing, and physical therapy.

C. Study Duration

To fully understand and assess all relevant patient outcomes, we generally recommend a 2-year follow-up spinal fracture study. FDA considers these devices used in the surgical (open or percutaneous) treatment of these fractures as permanent spinal implants because they are present in the patient's spine for 30 days or more. 21 CFR 812.3(d). We recommend that the follow-up evaluations occur at regular intervals with non-abutting, defined windows. The number and nature of these evaluation timepoints may differ depending on the design and purpose of your device.

D. Effectiveness Endpoint Evaluations

We recommend that you measure and report primary and secondary effectiveness parameters at each time point. We recommend that you include the specific parameter scales and methods of interpretation with your rationale and validation.

We recommend that the primary effectiveness parameters include:

- pain and function, using such tools as the pain scales, function/disability questionnaires (e.g., Visual Analog Scale (VAS), Neck Disability Index, Roland-Morris Disability Questionnaire, Oswestry Disability Index)
- maintenance or restoration of vertebral height or alignment, using specific radiographic criteria.

We recommend that the secondary effectiveness parameters include:

- health related quality of life, using validated applicable scales (e.g., SF-36 Health Survey, disease or age specific, i.e., osteoporosis or elderly quality of life questionnaires.)
- ambulatory status, which should be maintained or improved.

E. Safety Endpoint Evaluations

To assess the safety of your device, we recommend that you report <u>all</u> complications, whether believed to be device related or not, and whether the complications are anticipated or not, including:

- infection
- secondary surgical interventions
- neurological complications
- serious adverse events
- death.

In addition to the above, we recommend that you report the following radiographic evaluations:

- material extravasations into vascular or adjacent structures

- adjacent fractures or any other vertebral body fractures above and below the treatment site
- osteolysis surrounding the implanted material
- fracture through the material at the level of repair
- adjacent arthritis
- progression of disease
- fusion at the level of treatment.

We also recommend that you perform comprehensive neurological evaluations[6] at each timepoint due to the potential risks of spinal cord or neural injury associated with the proximity and vulnerability of the spinal cord and nerve roots. We recommend that you report:

- any complaint of symptoms which results in an unscheduled visit
- when a patient presents with new or worsening pain, neurological, and/or functional symptoms as compared to a previous visit
- any decompressive surgical intervention that was necessary.

F. Patient and Study Success Criteria

Patient and study success rates should be provided at each evaluation timepoint (e.g., 6 months, 12 months, 24 months).

Patient Success

The success criteria for an individual patient should be based on a clinical meaningful level of improvement (e.g., pain and function). This may be equivalent to a statistically meaningful level of improvement. For some of the more commonly used scales, one of the two may be used. However, these may not be applicable to the intended goal of the study and, therefore, you should provide a rationale. Patients should be no worse after the treatment. Therefore, we recommend that you base the success of a treatment on the following:

- success in each of the primary effectiveness parameters
- no secondary interventions.

We recommend that, depending on the proposed patient population, that you include the study design, and study goals, or other assessments (e.g., ambulatory status).

Study Success

We recommend that you base study success on a comparison of the treatment group to the control for the following:

- the intention and claims made for the treatment

[6]Refer to Section 9.2 of **Guidance Document for the Preparation of IDEs for Spinal Systems**[2] for additional details regarding neurological examinations.

- the study goals (e.g., superiority or equivalency)
- all primary effectiveness parameters and safety information (i.e., patient effectiveness).

G. Risk Analysis

Manufacturers of vertebral augmentation devices must conduct a risk analysis in accordance with design control requirements. 21 CFR 820.30(g). We recommend that you address all potential complications associated with your device in the risk analysis.

Vertebral augmentation devices discussed in this guidance are known to result in some serious complications in the patient population as demonstrated by medical device reports (MDRs) and literature reports. Some serious complications that you may want factor into your risk analysis include:

- hypotension
- hypoxemia
- abdominal and gastrointestinal adhesions
- cardiac arrhythmias
- myocardial infarction
- cardiac arrest
- pulmonary embolism (fat or cement)
- death.

We also recommend that your risk analysis take into account the complications, which have been associated with the components of the device, device delivery, percutaneous access, or the patients' underlying condition(s):

- adhesions/stricture of the ileum due to heat released during polymerization
- adjacent vertebral collapse due to osteoporotic disease
- adverse tissue reaction
- anaphylaxis
- bladder fistula
- bronchospasm
- bursitis
- cement extrusion into soft tissue
- deep wound infection
- complications/skin burns from fluoroscopy exposure
- dysuria
- hematoma
- hematuria
- hemorrhage
- heterotopic bone formation

- intercostal neuralgia
- local neuropathy
- local vascular erosion/occulusion due to cement impingement
- nerve entrapment/dysphagia due to extrusion of bone cement
- nerve root pain
- neuritis pain/loss of function
- pedicle fracture
- pneumonia
- pulmonary infection
- pyrexia/allergic pyrexia
- radiculopathy
- rib fracture in subjects with diffuse osteopenia due to downward force exerted during needle insertion
- sciatica
- short-term cardiac irregularities
- spinal cord compression with paralysis/loss of feeling
- stroke
- superficial wound infection
- thrombophlebitis
- transitory blood pressure decrease
- transitory worsening of pain due to heat.

5. Study Monitoring

In designing your studies with vertebral augmentation devices intended for the treatment of spinal insufficiency fractures, we recommend that you develop a comprehensive monitoring plan for these studies. Please note that sponsors are required to include written monitoring procedures in applications for investigational device exemptions (21 CFR 812.25(e)). Experience has shown that if sponsors make adequate provisions for monitoring studies, quality of the studies and data will follow. Therefore, we recommend:

- selecting qualified monitors
- ensuring investigator adherence to the investigational plan and other requirements
- ensuring investigator compliance in regard to record keeping and reporting.

6. Conclusions

This guidance may assist manufacturers in developing a vertebral augmentation device when its formulation or use parameters warrant a clinical trial. In addition, a pre-submission meeting with FDA to discuss questions regarding your device, intended use, clinical study design or other concerns may be appropriate and helpful. Devices that meet the criteria described in the

guidance entitled, **Expedited Review of Premarket Submissions for Devices**[7] may be a candidate for an expedited review. Well-organized submissions that address special controls and include a through clinical data presentation can aid FDA in completing its review.

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[7] http://www.fda.gov/cdrh/mdufma/guidance/108.html

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